REMARKS

A. Support for Amended Description of the Drawings

Applicants have herein above amended the description of Figures 6a through 6j; Figure 8a through 8c; and Figure 9a through 9j. Support for the amended description of Figures 6a through 6j is to be found in paragraphs 23 through 32, respectively, of the substitute specification filed on January 24, 2002. Support for the amended description of Figures 8a through 8c (*i.e.*, paragraph 34) is to be found *inter alia* in the description at paragraphs 34, 58 and 59 and in Table 2 of the substitute specification filed on January 24, 2002. Support for the amended description of Figures 9a through 9c (*i.e.*, paragraph 35) is to be found *inter alia* in the description at paragraph 35 and in Table 2 of the substitute specification filed on January 24, 2002.

2. Support for Amended Drawings

The instant amendments to drawings sheets 6/29 through 15/29 merely modify the labeling of the drawings sheets for consistency with the remaining drawings sheets on file. Accordingly, the amended drawings sheets are fully supported by the corresponding drawings sheets on file.

3. Support for Amended Claims

Claims 14 to 34 were pending in the application. Applicants have herein above canceled claims 15 and 34, and amended claims 14, 24, 27 and 33 and added new claim 35. Accordingly, claims 14 to 33 and 35 are now pending and presented for examination.

Support for new claim 14 is to be found *inter alia* in pending claim 14 and cancelled claim 15. Support for new claims 24 and 27 is to be found in the corresponding pending claims

24 and 27. Support for new claim 33 is to be found *inter alia* in pending claim 33 and canceled claim 34.

Support for new claim 35 is to be found *inter alia* in the description at paragraph 5 in relation to "minimal" epitopes free of sequences that flank the CTL epitopes; in Figure 1 and Figure 5 of the application as originally filed in relation to contiguous CTL epitopes; in Figure 5 in relation to intervening sequences (*e.g.*, the spacer sequence TS positioned between the epitopes YPHFMPTNL and SGPSNTPPEI); at paragraph 37 in relation to the absence of a methionine in the intervening sequence of the encoded polytope; and in the description at paragraphs 37 to 39 which demonstrates efficient expression of the claimed nucleic acid, processing of the encoded polytope protein to produce minimal CTL epitopes, and CTL recognition of the processed epitopes.

In view of the foregoing remarks, applicants respectfully submit that the instant amendments introduce no new matter for consideration and request that the amendments be entered.

4. Objection to the Disclosure

At paragraph 3 of the Office Action, the Examiner has objected to the disclosure on the basis that the Brief Description of drawings on page 5 no longer matches with the newly submitted figures. The Examiner also noted that the format of labeling for the figures, in particular Figures 8a-c and 9a-j (lower case) do not match that a Figures 6A-J (upper case).

In response to this objection, applicants have herein above amended the description of Figures 6a-j, Figures 8a-c, and Figures 9a-j at paragraphs 23-32, 34 and 35; and the corresponding references to these drawings sheets at paragraphs 47, 60 and 68, for consistency

with the filed drawings. Applicants have also amended the labelling on drawings sheets 6/29 through 15/29 for consistency with the labeling of the remaining drawings.

The Examiner is respectfully requested to reconsider and withdraw the objection to the disclosure in view of the foregoing amendment.

5. Rejections Under 35 USC §112, First Paragraph

A. Lack of Enablement

At paragraph 5 of the Office Action, the Examiner has rejected claims 14-34 on the basis that the specification "while being enabled for a recombinant vaccine CTL polyepitope-based composition comprising a polynucleotide encoding CTL epitopes as depicted in Figure 5 derived from pathogens MCMV, influenza, EBV, Adenovirus, and EG7 tumor for use as vaccines, does not reasonably provide enablement for vaccine compositions and their use in vaccination against any HIV."

In response to this objection, applicants have herein above amended claim 27 without prejudice to delete any reference to HIV, thereby obviating this rejection by the Examiner. The Examiner is respectfully requested to reconsider and withdraw the rejection in view of the foregoing amendment.

B. Lack of Written Description

At paragraph 6 of the Office Action, the Examiner has maintained the rejection of claims 14-34 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner states that the only disclosed use of the claimed polynucleotides is for a vaccine, and

that not all CTL epitopes, whether disclosed or undisclosed, are useful for a vaccine for preventing disease. The Examiner also considers that the specification provides an insufficient number of species of polynucleotide comprising a nucleic acid sequence encoding a plurality of CTL epitopes for a vaccine against HIV to describe the claimed genus.

In response to this objection, applicants have herein above amended claim 27 without prejudice to delete any reference to HIV. The claims therefore no longer encompass vaccines against HIV.

Applicants also maintain that a skilled artisan will recognize from the disclosure that *any* CTL epitope may be useful in the present invention, dependent upon the validity of the epitope(s) in eliciting CTL activity *in vivo*, and that, given the teaching provided in the specification as originally filed any one of the exemplified CTL epitopes may be substituted with any other CTL epitope known at the filing date.

In particular, applicants respectfully submit that the exemplified polyepitope-encoding constructs, which encode combinations of CTL epitopes from murine mytomegalovirus, lymphocytic choriomeningitis, influenza virus, Epstein-Barr Virus (EBV), Adenovirus, and ovalbumin, provide sufficient representation of structurally and functionally diverse CTL epitopes to demonstrate the requisite possession of the invention to the skilled artisan. Given the diverse nature of the CTL epitopes included in the exemplified polyepitope-encoding construct, the skilled person would be aware immediately of the general applicability of the present invention to eliciting CTL responses against any combination of structurally and functionally diverse CTL epitopes, and not merely those exemplified. As stated at paragraphs 51, 76 and 77 of the specification

51. Polytope constructs containing multiple CTL epitopes from various pathogens restricted by various MHC alleles are clearly capable of generating primary CTL responses to each epitope within the polytope vaccine. This has clear application in all vaccines where CTL responses are required for protection....

76. As will be apparent to those skilled in the art the present inventors have shown that the natural flanking sequences of CTL epitopes are not required for Class I processing, that is each epitope within the polyepitope protein was always efficiently processed and presented to appropriate CTL clones by autologous polyepitope vaccinia infected target cells.

77. As discussed above the present invention can be used with a range of epitopes. A range of epitopes are now available on an internet address which is described by Brusic *et al.,* Nucleic Acids Research, 1994, 22: 3663-5.

In fact, Brusic *et al.* describe the MHCPEP database, which is a curated database comprising over 4000 peptide sequences *known to bind MHC molecules*. Entries in MHCPEP are compiled from published reports as well as from direct submissions of experimental data. Each entry contains the source protein (when known), an estimate of binding affinity and critical anchor residues (if identified), and is fully referenced. The present format of the MHCPEP database allows test string matching searches.

With respect, given the exemplified teaching of the success of the claimed polyepitope-encoding constructs, the structural and functional diversity of the encoded CTL epitopes, and the specific and unmistakable directions to look for CTL epitopes in the MHCPEP database in the specification as originally filed, applicants maintain that the specification as filed contained a sufficient written description to demonstrate possession of the invention now claimed.

Moreover, applicants respectfully request reconsideration of the previous submissions in relation to the Cox Declaration and Exhibits JCC1 through JCC20 (*i.e.*, Exhibit V of the submission filed on November 25 2002), in particular:

(i) THAT the constructs provided by the specification are generic for constructs comprising two or more CTL epitopes, and, given the large number of CTL epitopes available at the filing date a skilled researcher in the field of vaccine delivery, bacteriology and virology, desirous of constructing a composition for use as a vaccine, would understand that the selection of appropriate epitopes for any particular vaccine application, and the incorporation of such epitopes into a polytope construct as provided by the inventors, would be routine in view of the skill in the arts and the guidance provided by the specification;

(ii) THAT the exact CTL epitopes incorporated into the constructs of the invention are not limiting because the invention concerns polytope constructs that contain two or more appropriate CTL epitopes lacking naturally occurring flanking sequences or methionine residues, wherein the encoded polytope protein is successfully processed to the individual component CTL epitopes which are expressed on the APC surface, induce CTL responses, and are recognized by pre-existing or induced CTL to cause killing of infected cells;

(iii) THAT the skilled artisan would readily appreciate from the teachings of the specification that such polytope constructs could comprise any number of contiguous or spaced CTL epitopes that do not include naturally occurring flanking sequences or methionine residues;

(iv) THAT the skilled artisan would find the manner of making the constructs of the present invention routine in view of the guidance provided in the specification, because the

materials and procedures for constructing the polytope constructs were readily available to the artisan at the time the application was filed;

(v) THAT ***both*** examples 1 and 2 of the application as originally filed show that the novel human and mouse constructs do, in fact, work, *i.e.* that CTL epitopes joined as directed by the specification are effectively processed, presented, and effective in inducing CTL responses to each epitope encoded by the polyepitope construct; and

(vi) THAT the skilled artisan would also appreciate that the examples provided are not limiting, and that the type of polytope construct as claimed by the Inventors would work for any combination of CTL epitopes.

Based on the wealth of publicly available information at the time the application was filed and the representative number of working examples provided in the specification as filed, applicants respectfully maintain that, in contrast to the Examiner's position, the specification as originally filed does convey to the skilled artisan that the inventors were in possession of the claimed genus.

The Examiner is respectfully requested to reconsider and withdraw the rejection in view of the foregoing amendment and remarks.

C. New Matter

At paragraph 7 of the Office Action, the Examiner has maintained the rejection of claims 14-34 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time that the application was filed, had possession of the claimed invention.

The Examiner states that amended claim 14 still recites "... CTL epitopes are contiguous or spaced apart by intervening sequences wherein said intervening sequences do not (i) comprise methionine or (ii) comprises naturally occurring flanking sequences of the epitopes," and that amended claim 33 still recites "CTL epitopes are contiguous or spaced apart by an intervening sequence that does not comprise methionine." The remaining claims stand rejected as being dependent on a rejected base claim.

In response to this rejection by the Examiner, applicants have herein amended claims 14 and 33 without prejudice to require a plurality of the CTL epitopes to be contiguous, thereby deleting references to the intervening sequence or a methionine residue from claims 14-33. Applicants respectfully submit that the amendment to these claims renders the rejection moot in respect of claims 14-33.

As for new claim 35, this claim merely recites that the encoded plurality of CTL epitopes are "contiguous or spaced apart by an intervening sequence that does not include a methionine." Applicants respectfully submit that the newly added claim is adequately supported by the description as stated *supra* and that no new matter rejection is applicable to this claim.

The Examiner also states that there is no support in the specification and claims as originally filed for the term "viral vector" in claim 21. Applicants respectfully traverse this rejection by the Examiner on the basis that the disclosure on page 3, paragraph 13 of the specification recites vaccinia virus vectors, avipox virus vectors and rhabdovirus vectors as representative examples of the class of virus vectors commonly available to the skilled artisan. Moreover, the specification cites Chatfield *et al.*, Taylor *et al.* and Hodgson *et al.* for additional information regarding suitable virus vectors. With respect, it would be clear to the skilled artisan that any known viral vector could be successfully used in the context of the present invention.

Proceeding on this basis, applicants maintain that, based upon what was known at the date of filing and the disclosure of three examples of viral vectors in the specification as filed, the specification satisfies the written description requirement with respect to viral vectors generally. The Examiner is respectfully requested to reconsider and withdraw the rejection in view of the foregoing remarks.

6. Rejections Under 35 USC §102(b)

A. Whitton et al.

At paragraph 9 of the Office Action, the Examiner maintains the rejection of claim 14 under 35 U.S.C. §102(b) as being anticipated by Whitton *et al.* The Examiner states that amended claims 14-15 still recite "at least two of the plurality of CTL epitopes are contiguous or spaced apart by an intervening sequence that does not comprise a methionine" and that the term "comprise" is open-ended language which expands the intervening sequence to include additional sequences at either or both ends of the intervening sequence. The Examiner also notes that the specification defines the term "substantially free of sequence naturally found to flank the cytotoxic T lymphocyte epitopes" to include 1-5 flanking amino acids, and state that the term "comprises" expands this flanking sequence to include additional residues.

In response to this rejection, Applicants have amended claims 14-33 without prejudice to require the CTL epitopes to be ***contiguous*** **and** ***free of sequences naturally found to flank the CTL epitopes***. In contrast, in the only case of linked CTL epitopes disclosed by Whitton *et al.* (*i.e.*, construct VVMG34, page 349, right col., first paragraph of Results Section), the encoded CTL epitopes were non-contiguous by virtue of (i) the introduced initiation methionine; and (ii) additional non-viral amino acids connecting the minigene products. Accordingly, whilst Whitton *et al.* may disclose CTL epitopes in close proximity, they do not disclose contiguous CTL

epitopes. With respect, the requirement in the amended claims for ***contiguous epitopes free of flanking sequences*** excludes the possibility of non-viral spacer sequences as disclosed by Whitton *et al.*

With particular regard to the Examiner's comment that the term "comprise" expands the CTL epitope to include additional amino acid residues at either or both ends, Applicants respectfully point out that such a construction in not possible in view of the requirement for ***contiguous epitopes free of flanking sequences*** in amended claims 14-33. Clearly, the introduction of additional flanking sequence would mean that the epitopes are non-contiguous.

New claim 35 requires the CTL epitopes to be minimal CTL epitopes and uses the term "a plurality of the CTL epitopes are contiguous or spaced apart by an intervening sequence that does not include a methionine." Applicants submit that the word "include" does not expand the intervening sequence to include additional sequences at either or both ends and, as a consequence, the rejection would not apply to new claim 35. Nor would it be an appropriate construction of claim 35 to conclude that any additional sequence at either or both ends could comprise a methionine residue, because any such additional sequence would still form part of the intervening sequence feature, which must, of necessity, not include a methionine. Accordingly, on any reasonable construction of new claim 35, the claimed nucleic acid clearly excludes the Whitton teaching, either by requiring contiguous epitopes, or by requiring any intervening sequence to not include a methionine. Accordingly, new claim 35 is clearly novel over Whitton *et al.*

Accordingly, the claims as presently amended are clearly novel over Whitton *et al.* The Examiner is respectfully requested to reconsider and withdraw the rejection in view of the foregoing amendment and remarks.

B. Lawson et al.

At paragraph 10 of the Office Action, the Examiner rejects claims 14-16, 20-22, 25, 27 and 33-34 under 35 U.S.C. §102(b) as being anticipated by Lawson *et al*, on the basis that the citation teaches a recombinant vaccinia expressing a full length HA polypeptide that inherently contains more than one CTL epitope. The Examiner also states that the epitopes disclosed by Lawson *et al.* are contiguous.

With particular regard to the Examiner's assertion that the CTL epitopes in the full-length HA polypeptide disclosed by Lawson *et al.* are contiguous, Applicants respectfully submit that the presence of multiple epitopes is not necessarily a disclosure of those epitopes being contiguous. With respect, the term "contiguous" requires juxtaposition of the minimum CTL epitope, a feature on which Lawson *et al.* is silent.

Without conceding the correctness of the Examiner's position and in order to advance prosecution, Applicants have herein above amended without prejudice claims 14 and 33 to require the epitopes to be ***contiguous and free of sequences naturally found to flank the CTL epitopes***. With respect, these limitations in amended claims 14-33 clearly exclude a full-length HA polypeptide as disclosed by Lawson *et al.*

With particular regard to new claim 35, this claim requires that "a plurality of the CTL epitopes are contiguous or spaced apart by an intervening sequence that does not include a methionine." Applicants respectfully maintain that the requirement for minimal CTL epitopes substantially free of flanking sequences in conjunction with the intervening sequence excludes a native protein as described by Lawson *et al.* Applicants further maintain that Lawson et al is silent on the presence of minimal CTL epitopes as claimed in claim 35. Conceptually, the positioning of nucleotide sequences encoding minimal CTL epitopes in claim 35 is entirely

different from the possible and unproven presence of CTL epitopes in a native protein. Accordingly, claim 35 is clearly novel over Lawson *et al.*

Accordingly, the claims as amended are clearly novel over Lawson *et al.* The Examiner is respectfully requested to reconsider and withdraw the rejection in view of the foregoing amendment and remarks.

7. **Rejection Under 35 USC §103(b)**

At paragraphs 13-21 of the Office Action, the Examiner rejects claims 14, 17-21 and 23-32 under 35 U.S.C. §103(a) as being unpatentable over Lawson *et al.*, in view of Whitton *et al.*, and in further view of Berzofsky *et al.*; or over Lawson *et al.*, in view of Del Val *et al.*, or Latron *et al.*, or Burrows *et al.*; or over Lawson *et al.*, in view of Panicali *et al.*; or over Lawson *et al.*, in view of Adams *et al.*; or over Lawson *et al.*, in view of Celis *et al.*; or over Lawson *et al.*, in view of Wildmann *et al.*; or over Lawson *et al.*, in view of Potter *et al.*

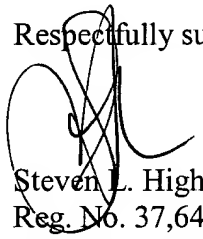
Applicants respectfully submit that the amended claims 14-33 obviate these rejections by the Examiner in respect of those claims, on the basis that none of the prior art citations mentions or suggests a polynucleotide encoding a plurality of contiguous CTL epitopes wherein each epitope is ***free of sequences that naturally flank the CTL epitope***.

Nor do any of the prior art documents alone or in combination mention or suggest a nucleic acid encoding a plurality of minimal CTL epitopes that are either contiguous or spaced apart by an intervening sequence that does not include a methionine. Accordingly, applicants respectfully submit that new claim 35 is also non-obvious over the citations.

8. Conclusion

In view of the above, Applicants respectfully submit that the claims are in condition for allowance. Applicants respectfully and earnestly request notification to that effect. The Examiner is invited to contact the undersigned attorney with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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